A Systematic Review on the Imaging Findings in Auditory Neuropathy Spectrum Disorder

(Basic Hearing Science)

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20AUD035

This Dissertation is submitted as a part of the fulfilment

for the Degree of Master of Science in Audiology

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August 2022

CERTIFICATE

This is to certify that this Dissertation entitled "**A Systematic Review on the Imaging Findings in Auditory Neuropathy Spectrum Disorder**" is bonafide work submitted as a part of fulfillment for the degree of Master of Science (Audiology) student with Registration Number 20AUD035. The Dissertation has been carried out under the guidance of the faculty of this institute. It has not been submitted earlier to any other University for the award of any other Diploma or Degree.

Mysuru
August, 2022

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CERTIFICATE

This is to certify that this Dissertation entitled " **A Systematic Review on the Imaging Findings in Auditory Neuropathy Spectrum Disorder** " is bonafide work submitted in part fulfillment for the degree of Master of Science (Audiology) student with Registration Number 20AUD035. The Dissertation has been carried out under my supervision and guidance. It has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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DECLARATION

This is to certify that this Dissertation entitled " **A Systematic Review on the Imaging Findings in Auditory Neuropathy Spectrum Disorder** " is a result of my study under the guidance of Dr. Chandni Jain, Associate professor in Audiology, Department of Audiology, All India Institute of Speech and Hearing, Mysuru. It has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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August, 2022

Dedicated to my parents and to my dear brother……

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Abstract

The present systematic review examines imaging findings in the Auditory Neuropathy Spectrum Disorder population (ANSD). For the systematic review, a literature search was done using electronic databases (e.g., Pub Med, Google Scholar, J Gate, Science direct) over the past twenty years. The retrieved articles were assessed in two stages: title and abstract screening, followed by a full-length article review. 19 articles were selected after the full-length review of 379 shortlisted articles. Among the selected studies, one was a cross-sectional study design, one case-control study, four case series, and the remaining were prospective cohort and retrospective cohort studies, respectively. Imaging in the selected studies was done using magnetic resonance imaging (MRI) and computerized tomography (CT). Most studies reported cochlear nerve deficiency (CND) as the most common abnormality in imaging findings. Also, MRI was the imaging modality of choice recommended in most studies. It was also noted that CND was a characteristic feature of unilateral ANSD. From this systematic review, it is clear that integrating imaging studies into diagnostic protocol would help to understand the underlying pathology better and expedite decision-making and intervention for ANSD patients.

Keywords; ANSD, Imaging, Computerised tomography, Magnetic resonance imaging, Cochlear nerve deficiency

Chapter 1

Introduction

Auditory Neuropathy Spectrum Disorder (ANSD) is a condition characterized by the abnormal function of inner hair cells (IHC), synapses, spiral ganglion neurons, and the auditory nerve itself (Starr et al., 2000). The prevalence of ANSD varies between 1 and 40 %, depending upon the study population (Berlin et al., 2010). It is thought that around 7–10% of all childhood permanent hearing loss is due to ANSD (Rance, 2005). ANSD is traditionally considered a bilateral and symmetrical condition, and only a few reports of unilateral conditions exist. Unilateral ANSD was diagnosed in approximately 1.31% to 7.31% of patients (Zhang et al., 2012), and recent reports evidenced about 2.4%–4.7% of unilateral ANSD (Usami et al., 2017).

Diverse etiologies can lead to ANSD, and multiple sites can involve in the pathological mechanism. Acquired and genetic factors contribute to ANSD (Berlin et al., 2010). ANSD can also occur as a part of various syndromes or non-syndromic hearing loss (Norrix & Velenovsky, 2014). Starr et al. (2000) have given ANSD classification based on different etiologies: (i)Type I includes postsynaptic auditory neuropathy (AN) as well as vestibular and peripheral neuropathies (ii)Type II postsynaptic involves AN and optic nerve lesions accompanying nuclear and mitochondrial mutations (iii) Type III includes presynaptic AN, inner hair cell (IHC), and neurotransmitter disorder (iv) Type IV ANSD wherein the pathological sites are not known.

1.1 ANSD and audiological characteristics

ANSD mainly comprises three events: first, the presence of otoacoustic emissions (OAEs) and or normal cochlear microphonics (CM) indicating normal outer hair cell (OHC) function; second, absent or perturbed auditory brainstem response (ABR) indicating that the transmission of afferent neural information from the IHCs to the brainstem pathways via the auditory nerve is disordered; third, absent or abnormal middle-ear muscle reflexes indicating the abnormal efferent feedback mechanism (Starr et al., 2000; Berlin et al., 2005). ANSD patients hearing thresholds range from normal hearing to profound hearing loss, and the hearing levels tend to fluctuate across evaluation (Rance and Starr, 2015). Most patients exhibit low-frequency hearing loss configuration and a poor correlation between pure tone thresholds and speech discrimination scores (Meethal et al., 2019). 70% of pediatric ANSD patients were reported with the disappearance of transient evoked otoacoustic emissions (TEOAEs) as the disease progressed (Kitao et al., 2019).

1.2 ANSD and radiological characteristics

Abnormal findings of the brain, posterior cranial fossa, and cochlear nerves, either developmental or acquired, are commonly seen in the ANSD (Roche et al., 2010). Inner ear abnormities are portrayed using Computerised tomography (CT) or Magnetic resonance imaging (MRI). Numerous abnormalities are identified in children diagnosed with ANSD using MRI that are not perceptible on CT. CT examination augments MRI when there are inner ear abnormalities or a narrow IAC. Cochlear nerve hypoplasia (CNH) and cochlear nerve aplasia (CNA) are regarded as cochlear nerve deficiency

(CND), which represents a severe and literal form of ANSD (Adunka et al., 2006; Adunka et al., 2007; Nakano et al., 2013).

Between 18% and 33 % of children with ANSD have CND, which is a greater prevalence than that reported for children with sensorineural hearing loss (SNHL) (between 6 % and 16.1 %) (Buchman et al., 2006; Roche et al., 2010; Walton et al., 2008). MRI shows a smaller cochlear nerve diameter than the nearby facial nerve, and CT indicates a narrow bony cochlear nerve canal (BCNC) is considered CND. The characteristics of unilateral ANSD appear to be mainly linked to CND (Zhang et al., 2012) .

There is a disagreement over the best imaging method and diagnostic standards for CND. MRI is preferable to CT for evaluating nerves, but CT is better for measuring the size of IAC and the BCNC. CT identifies bony abnormalities but cannot identify nerves (Adunka et al., 2007). As CND can occur with normal bony anatomy, MRI is mandatory for visualizing these nerves. CT can be beneficial in delineating important abnormal bony landmarks such as a narrowed IAC or CNC or an aberrant facial nerve canal. Since CND can happen with a normal bony structure, an MRI is required to see these nerves. To identify a stenotic IAC or CNC or an atypical facial nerve canal, CT is beneficial.

Walton et al. (2008) reported that cochlear nerve deficiency affects cochlear implant outcomes in ANSD patients. Morita et al. (2004) reported that the cochlear nerve identified on MRI was necessary to establish whether cochlear implants provided

satisfactory outcomes. Thus, CND has been related to poor cochlear implant performance.

1.3 Need for the Study

Studies have demonstrated that examining the cochlear nerve can predict the success and viability of cochlear implantation in ANSD neonates with CNH or CNA (Jeong & Kim, 2013). CT may miss cochlear nerve aplasias, which can be confirmed on MRI. Therefore, determining the status of CN is crucial to proceeding with ANSD management. Moreover, a thorough knowledge of the clinical profile, electrophysiologic results, and accurate interpretation of an MRI of the brain, IACs, and labyrinth are also necessary for identifying the condition. It is crucial to identify ANSD characteristics with early OAE and CM. If the electrophysiological evaluation reveals ANSD features, CND's probability should be ruled out. Based on imaging findings, the most efficient hearing rehabilitation must be determined to set realistic expectations for parents and guardians and differentiate between ANSD with a normal cochlear nerve and CND. However, little attention is paid to imaging findings or the need for radiological assessment in patients exhibiting ANSD. Early detection of ANSD through newborn hearing screening and subsequent referral for a comprehensive audiological and radiological assessment is important. Hence there is a need to understand various imaging findings in the ANSD population for the correct etiologic diagnosis. Thus, this review will provide insight into imaging findings in ANSD, which would help audiologists to predict the prognostic factors and the right line of rehabilitation.

1.4 Aim of the Study

The present study systematically reviewed the imaging findings in Auditory Neuropathy Spectrum Disorder.

1.5 Research Questions

1. Will there be imaging abnormalities in the ANSD population?
2. If yes, what are the common imaging abnormalities seen in ANSD?
3. What is the different imaging protocol used for the etiology-based diagnosis of ANSD?
4. Is cochlear nerve deficiency a characteristic feature of unilateral ANSD?

Chapter 2

Methods

2.1 Research Design

The Preferred Reporting Items for Systematic Review and Meta-analyses statement (PRISMA) criteria were used to conduct the systematic review.

2.2 Eligibility criteria to select the studies for systematic review

For the systematic review, studies were selected based on the quality of the method, data, intervention, and outcome. The following criteria were followed for the selection of studies.

Inclusion criteria:

- Articles published in peer-reviewed journals over the past twenty years were included.
- For the systematic review, studies were selected based on the quality of the method, data, intervention, and outcome.
- Original articles including human subjects with adequate samples and relevant statistics were considered.
- Only articles published in the English language were considered for the review.

For the systematic review, the PECOS review question was used, which included:

Participant- ANSD population

Exposure- Radiological tests

Control- Normal hearing peers/SNHL

Outcome- Results obtained from the radiological test

Exclusion Criteria:

- Articles with poor methodological quality or articles other than the English language were excluded.
- Reports including animal studies were excluded.

2.3 Search strategy

A systematic search was conducted in the following electronic databases (Pub med, Google Scholar, J gate, Science Direct) published over the past twenty years using Boolean operators such as 'AND,' 'OR' 'NOT.' The keywords used for the search string for all databases were 'Auditory neuropathy,' 'Dysynchrony,' 'ANSD,' imaging,' 'Auditory neuropathy spectrum disorder,' 'cochlear nerve,' 'radiology,' 'MRI,' 'CT,' and 'cochlear nerve deficiency.

2.4 Data extraction

The search results were combined using the Rayyan QCRI (Qatar Computing Research Institute) and Mendeley desktop reference manager system, and the duplicate studies were eliminated. The studies that met the inclusion criteria were identified by screening the titles and abstracts retrieved from the search strategies. After that, the full text of the potential studies was retrieved and matched to see if they were eligible. The extracted data included: article title, author details with their affiliation, year of publication, research design, study population, sample size, age group, comparison group, method of outcome measures, and keywords specific to imaging findings in ANSD.

2.5 Methodological quality appraisal

The studies included in the systematic review were subjected to a methodological quality assessment. We used the National Institute of Health (NIH) Quality assessment tool for observational cohort and cross-sectional studies, case-control studies, and case-series studies for the chosen studies. The following criteria: design, research population, sample bias, information gathering, variables, blinding, and dropouts were all covered by the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional studies. The NIH Quality Assessment Tool for Case-Control studies includes design, target population, selection bias, information gathering, information on the case and control separately, measures of exposure, blinding, and key potential confounding variables. The NIH Quality Assessment Tool for Case-series studies includes design, target population, information gathering, and information on case exposure and outcomes. Based on the above parameters, an overall rating of 'good,' 'fair,' or 'poor' was given. All studies were rated individually.

Chapter 3

Results

The present study aimed to do a systematic review of the imaging findings in ANSD. A total of 379 articles were obtained after reviewing through all the databases, of which 72 duplicates were eliminated. The titles and abstracts of the remaining 307 articles were screened to exclude 252 articles as they did not fulfill the review objectives. Thus, 55 articles were included for the next step. Full-text articles were retrieved for the 55 shortlisted abstracts. Based on the inclusion criteria, 19 articles were included for the data extraction and final review. Figure 3.1 shows the schematic representation of the systematic search process.

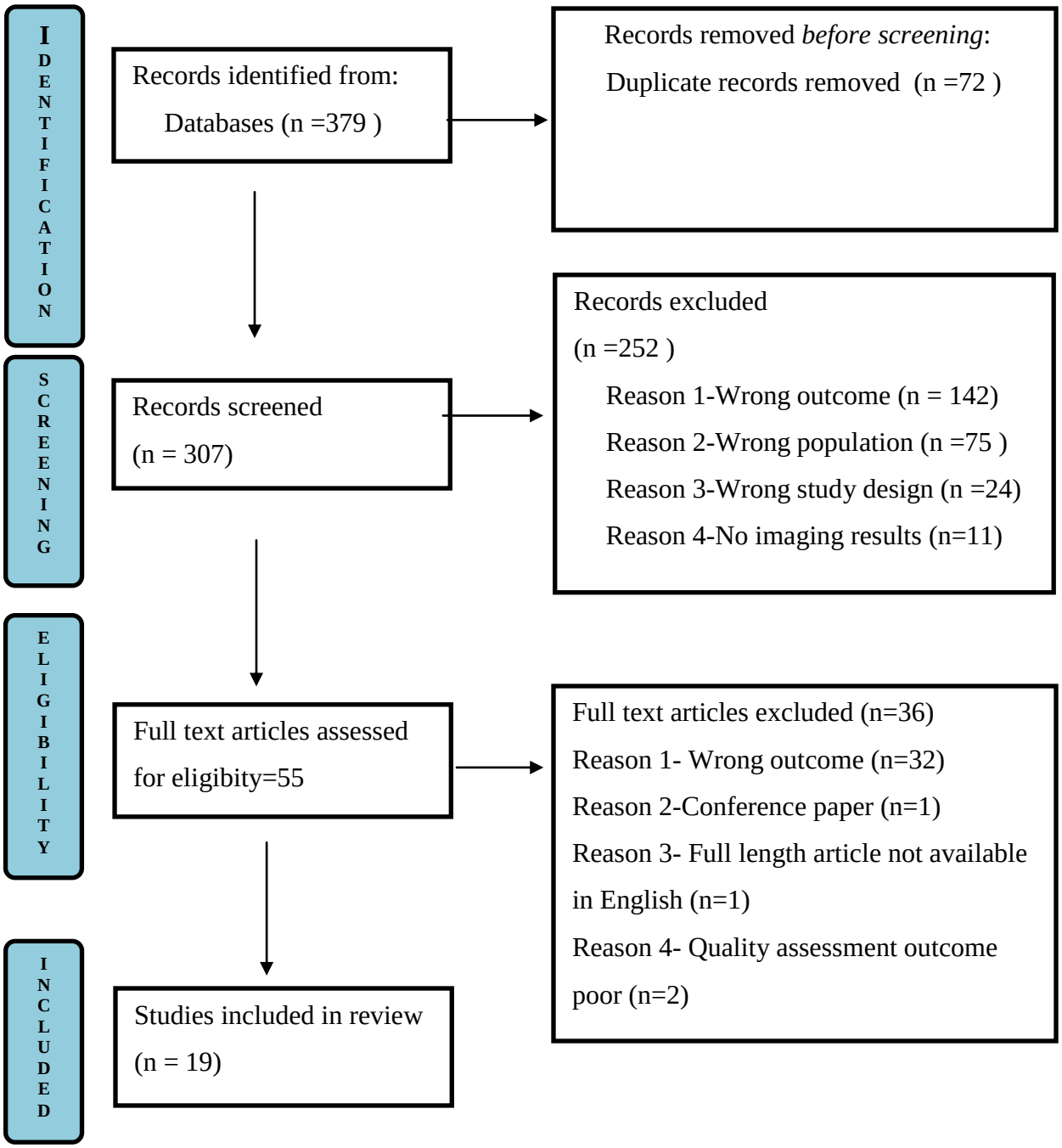

Figure 3.1 PRISMA flow chart of search results

3.1 Results of Data Extraction

Table 3.1 shows the aim of the study, study design, details of the participants, the audiological and radiological tests used in the study, and the results for each study included in the systematic review.

Table 3.1

The details of participants, the audiological and radiological tests used in the study, and the results for each study included in the systematic review.

Author and Year	Aim of the Study	Study design	Population Type	Method	Results
Laurent et al. (2022)	To explore the audiological characteristics as well as vestibular, and radiological findings of children with UANSD.	Cohort	**Study group**: 22 UANSD children (12 boys and 10 girls) **Age Range**: 0-95 months	**Audiological assessment**: Tympanometry, DPOAE, TEOAE, AEP **Vestibular assessment:** cVEMP, vHIT, Caloric testing **Imaging assessment**: 1.5 T MRI. The focus was on IAM. Sequences used: coronal and axial T2 weighted and sagittal and axial T1 weighted	• Out of 22 UANSD,18 children underwent MRI, and the findings are as follows: 15 patients- CNA; 2 patients-CNH. • 7 patients had additional abnormalities such as: 3-vestibular dysplasia; 2- VN anomalies, 1-absent SCCs, and 1-homolateral brainstem hypoplasia.

Song et al. (2021)	To investigate the characteristic features of patients with UANSD.	Cohort	**Study group**: 44 patients (mean age, 4.35 ± 4.39 years; 22 males and 22 females) with UANSD	**Audiological Tests**: PTA, BA, Immittance, ABR, ECochG, ASSR and 40Hz AERP. **Imaging assessment:** 1.5 T MRI	• 18 underwent MRI, and the findings were: 7-CND (4- CNA, 3-CNH) and 11- normal MRI.
Lin et al. (2020)	To study the etiology and auditory characteristics of children with ANSD and the prognostic utility of ASSR.	Cohort	**Study group**: 101 ANSD children: 57 boys and 44 girls.	**Audiological assessment:** DPOAE, ABR, ASSR, BA**.** **Imaging assessment:** • Non-contrast brain MRI was done to assess the central auditory pathway and CN. Temporal bone HRCT was done with contiguous axial and coronal sections to evaluate IE.	• Out of 83 patients who underwent imaging, 11 – CND (8-CNA, 3CNH);1-IE malformation. • CNS abnormalities were: 7-Cerebral hypomyelination (one due to genetic etiology), 1- Diffuse parenchymal loss, and 9-thin corpus callosum. • Of the total ANSD patients, comprised

					CND as etiology in 10.9%.
Meethal et al. (2019)	To study the audiological findings and causes associated with ANSD	Cross-sectional Study	**Study group**: 42 ANSD patients: 21 patients = 11–20 years, 13 patients were between 0 and 10 years, and the remaining eight were aged above 20 years. (mean age of 10.35 ± 2.10 years)	**Audiological assessment:** PTA, speech audiometry, immittance, OAE, and ABR. **Imaging assessment:** MRI brain with IE– focusing on structural anomalies; cochlea, vestibulocochlear nerve, and the IAC was done.	• MRI data of all the patients revealed no inner ear abnormalities (100%).
Rajput et al. (2019)	To study aetiologies of ANSD in children	Cohort	**Study group:** 92 children diagnosed with ANSD.	Recruited pediatric ANSD patients from four CI programs retrospectively. Documented the age at diagnosis, comorbid conditions, and predisposing factors.	• MRI revealed: 33-CND cases; 29- cerebral abnormality; 14 - widened vestibular aqueduct; 10- vestibular dysplasia;

				Imaging assessment: MRI: IAMs and brain	5- cochlear dysplasia respectively, and 34- other miscellaneous peripheral anatomical abnormalities. • CND was the most common finding
Wang et al. (2017)	To characterize the radiological appearance of the modiolus in ANSD patients	Case series	**Study group**: Seven pediatric cochlear implantees with ANSD. **Comparison group**: 15 pediatric implantees with SNHL	**Imaging assessment**: Preoperative HRCT of temporal bone and MRI was done, and the mid-modiolar cut was seen for image analysis. -Attenuation measurement of the modiolus's midpoint, the cochlea's middle turn, was performed using HU	• Higher attenuation values (796.2±53.0HU) for ANSD patients than a similar control group with SNHL(267.1±45.6 HU) were statistically significant, indicating less ossification in the comparison group.
Peng et al. (2016)	To assess the diameter of CN in adults with ANSD using MRI and to see	Cohort	**Study group**: 24 adult ANSD patients (26.5 +/- 6.3) **Control**: 20 non-	**Imaging assessment** MRI retrospectively examined 3-T MRI done. 3D FIESTA was performed.	• More significantly smaller LD, SD, and CSA of CN and FN were observed in ANSD patients than in

	whether CND is one of the causes of ANSD		ANSD SNHL (32.2 +/- 4.1) and 24 normal hearing subjects (23.5 +/- 2.3)		control groups. • Hence, CND can be a primary lesion for ANSD
Ai et al. (2016)	To establish the relationship between ANSD and IAC stenosis	Case-control	**Study group**: 21 children (nine females and 12 males) with congenital SNHL and inner auditory canal stenosis. **Age Range**:11 months- 6 years. Mean age- 3.4 years **Control:** 10 children with ANSD with no congenital malformation	**Audiological assessment:** DPOAEs, ABR, BA **Imaging assessment** HRTB CT identified all the children with stenotic IAC. 3T MRI of the IE and MRI of the brain to rule out white matter lesions.	• ANSD characteristics were seen in 30 of the 37 ears, with IAC stenosis accounting for 81.1%. • Also, of the 37 ears, 32 ears with IAC stenosis had CND.

Boudewyns et al. (2016)	To explore the prevalence, risk factors, cause, and management of ANSD in children	Cohort	13 ANSD children (6 UANSD and 7 Bilateral ANSD)	**Audiological assessment** OAE, ABR **Imaging assessment** MRI	• MRI results showed: 5 patients-CND (1-Bilateral ANSD, 4-UANSD); • 1-arachnoidal cyst at CPA compressing VIII nerve (UANSD)
Mohammadi et al. (2015)	To investigate whether any underlying structural abnormality could describe the etiology of ANSD	Case series	**Study group:** 17 neonates with UANSD (10 Males, 7 females)	**Audiological assessment:** DPOAE, ABR, Tympanometry **Imaging assessment:** CT and/or MRI	• Out of 11 cases who underwent CT, abnormalities identified were: 3- narrowed IAM; 1-transverse bony bar in the IAM ; 1-slight rotation of the temporal bone and 1-low density pericochlear change; 5-normal CT. • MRI showed: 8-CNA, 1-vascular loop by AICA,1-in utero CMV

					• Using MRI, three additional cases were identified, which were missed in CT.
Levi et al. (2013)	To explore the characteristics exhibited by children with CND	Cohort	**Study group:** 18 children with CND. **Age Range**: 2 weeks – 8 years	Retrospectively reviewed data of children with CND. **Imaging assessment:** 3 -T MRI	• Thirteen exhibited ANSD profile, accounting for 72%. • Half of the participants also had various IE abnormalities such as stenotic IAC, hypoplastic FN, absent inferior VN, horizontal SCC absent, posterior SCC absent, superior SCC dilated, dilated vestibule, EVA, cystic cochlea, and a common cavity and comorbidities.
Jeong and Kim (2013)	To examine the role of	Cohort	**Study population:**	**Audiological assessment:** CAP	• Results showed: Five patients-narrow or

	preoperative radiological results on the long-term CI outcomes		15 children with ANSD.	IT-MAIS MWT **Imaging assessment** HRCT MRI 1.5T	obliterated BCNC and absent CN ; 9-normal BCNC and CN
Liu et al. (2012)	To establish a relationship between CND and UANSD	Case series	**Study group:** 85 profound SNHL- 46 males and 39 females. **Age Range**: 1-26 years	**Audiological assessment:** PTA,Tympanogram,OAE, ABR **Imaging assessment** MRI-Direct and reconstructed sagittal oblique images of the contents of the IAC	• Out of the total 85 cases, eight were identified as having UANSD and the MRI findings reveal absent CN for all except one with small CN.
Maris et al. (2011)	To retrospectively review the prevalence of ANSD in neonates who failed the screening	Case series	**Study group:** 135 infants who failed UNHS	**Audiological assessment** TEOAE, ABR **Imaging assessment** MRI of posterior fossa	• Out of 135 referred cases, 4-UANSD and MRI showed aplasia or CNH in them.

Roche et al. (2010)	To describe the imaging findings in ANSD	Cohort	**Study group:** 118 ANSD children	**Audiological assessment** OAE, ABR **Imaging assessment** CT and 1.5 T MRI	• MRI findings revealed: 51-CND; 42- brain abnormalities and 33-prominent temporal horns. • CT revealed 13 cochlear dysplasia
Huang et al. (2010)	To examine whether CND is related to brain or inner ear abnormalities in children with ANSD	Cohort	**Study group:** 113 ANSD children **Age Range:** 11 weeks to 13.5 years. (mean age of 2.31 ± 2.58 years)	**Imaging assessment**: A 1.5 T or 3 T MRI was used. Axial and sagittal temporal bone images were seen. An image review of cranial MR was done to examine brain or CSF space abnormalities.	• Of 113 patients,103 underwent cranial MRI, and the result showed: 34 -CND (14.6% bilateral and 18.4 % unilateral). • CND in CHARGE syndrome (1 unilateral and 1 bilateral) and in 1 Rett syndrome (bilateral) • Labyrinthine and hindbrain abnormalities were closely associated with bilateral CND in

					ANSD, which was statistically significant.
Teagle et al. (2010)	To describe the preoperative, surgical outcomes, and post-operative CI performance of children with ANSD	Cohort	**Study population:** 58 CI implanted children with ANSD (50 bilateral ANSD, 8 UANSD)	**Audiological assessment:** Immittance, OAE, ABR, PB-K, and MLNT or LNT and behavioral testing. **Imaging assessment:** Preoperative MRI and Selective use of HRCT	• Results showed 23 abnormalities on MRI, including : 7-periventricular leukomalacia; 9 - CND in at least one ear; 2 - Dandy-Walker malformation; 3- severe IE malformations including cochlear hypoplasia, 1- Arnold Chiari type II malformation; and optoinfundibular dysplasia.
Walton et al. (2008)	To evaluate the CI performance in children with ANSD and CND compared to	Cohort	**Study population:** 54 Children with ANSD	**Audiological assessment:** EABR, Melbourn speech perception test **Imaging assessment** MRI-Axial T1, T2, and fluid-	• 15 children had CND with ANSD. • Also, they had associated IE abnormalities

	ANSD with normal cochlear nerve			attenuated inversion recovery sequences.	
Buchman et al. (2006)	To describe the characteristics of children with ANSD associated with CND	Cohort	**Study group:** 65 children with ANSD	**Audiological assessment** ABR, OAE, ASSR Behavioral testing **Imaging assessment** MRI and or CT	• MRI revealed: 9-CND (5 unilateral and 4 bilateral) • Children with CND can exhibit ANSD characteristics.

Note: UANSD-Unilateral auditory neuropathy spectrum disorder, DPOAE-Distortion product otoacoustic emission, TEOAE-Transient evoked otoacoustic emissions, AEP-Auditory evoked potential, Cvemp- Cervical evoked myogenic potential, vHIT-video head impulse test, MRI-Magnetic resonance imaging, IAM- Internal auditory meatus, CNA-Cochlear nerve aplasia, CNH-Cochlear nerve hypoplasia, PTA-Pure tone audiometry, BA-Behavioral audiometry, ABR-Auditory brainstem response, ECochG-Electrocochleography, ASSR-Auditory steady-state potential, AERP-Auditory event-related potential, CND-Cochlear nerve Deficiency, UAN-unilateral auditory neuropathy, SNHL-Sensorineural hearing loss , HRCT-High resolution computerized tomography, HU-Hounsfield units, LD-Long diameter, SD-Short diameter, CSA-Cross sectional area, FN-Facial nerve, AICA-Anterior inferior cerebellar artery, SCC-Semicircular canal, IE-Inner ear, EVA-enlarged vestibular aqueduct, CPA-Cerebellopontine angle, CAP-Categories of auditory performance, IT-MAIS-Infant toddler meaningful auditory

integration scale, MWT-Monosyllabic word test, BCNC-Bony cochlear nerve canal, CN-cochlear nerve, IE-Inner ear, VN-Vestibular nerve, CMV-Cytomegalovirus, WM-White matter

3.2 Quality Assessment

Quality assessment of the selected studies for the systematic review was done using the National Institute of Health (NIH) Quality assessment tool (APPENDIX A, B, and C). All the research chosen had defined aims and objectives, and the methodological quality ranged from good to fair. Among the 19 studies, one was a cross-sectional study design, one case-control study, four case series, and the remaining were prospective cohort and retrospective cohort studies, respectively. Almost all studies clearly defined the outcome measures, which proved valid and reliable in most situations. The details of the quality assessment tool are given in Tables 3.2, 3.3, and 3.4, respectively.

Table 3.2

Quality assessment tool for Observational Cohort and Cross-Sectional studies

Authors/Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Outcome
Laurent et al. (2022)	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	Yes	NA	Yes	NR	NA	No	**GOOD**
Song et al. (2021)	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	Yes	NA	Yes	NR	No	No	**GOOD**
Lin et al. (2020)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NR	Yes	No	**GOOD**
Meethal et al. (2019)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	NR	NA	No	**GOOD**
Rajput (2019)	Yes	Yes	Yes	Yes	No	NA	Yes	NA	Yes	NA	Yes	NR	NA	No	**FAIR**
Boudewyns et al. (2016)	Yes	Yes	NA	Yes	No	NA	Yes	NA	Yes	NA	Yes	NR	NA	No	**FAIR**
Peng et al. (2016)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	Yes	NA	No	**GOOD**
Levi et al. (2013)	Yes	Yes	Yes	Yes	No	Yes	NA	NA	Yes	NA	Yes	NR	NA	NR	**FAIR**
Jeong & Kim (2013)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	NR	NA	Yes	**GOOD**
Roche et al. (2010)	Yes	Yes	Yes	Yes	No	NA	NA	NA	Yes	NA	Yes	Yes	NA	Yes	**GOOD**
Huang et al. (2010)	Yes	Yes	Yes	Yes	No	Yes	NA	NA	Yes	NA	Yes	Yes	NA	NR	**GOOD**
Teagle et al. (2010)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	No	Yes	NA	Yes	No	**GOOD**
Walton et al. (2008)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	NA	Yes	**GOOD**
Buchman et al. (2006)	Yes	Yes	Yes	Yes	No	Yes	NA	NA	Yes	NA	Yes	NR	NA	No	**FAIR**

Table 3.3

Quality assessment tool of Case-Control Studies

Authors/Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Outcome
Ai et al. (2016)	Yes	Yes	No	Yes	Yes	Yes	NA	NR	Yes	Yes	NR	NR	**FAIR**

Table 3.4

Quality Assessment Tool for Case Series Studies

Authors/ Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Outcome
Wang et al. (2017)	Yes	Yes	Yes	NA	Yes	Yes	NR	No	Yes	**FAIR**
Mohammadi et al. (2015)	Yes	Yes	Yes	Yes	Yes	Yes	NR	NA	Yes	**GOOD**
Maris (2011)	Yes	Yes	Yes	Yes	Yes	Yes	NR	NA	Yes	**GOOD**
Liu et al. (2011)	Yes	Yes	Yes	NA	Yes	Yes	NA	NA	Yes	**FAIR**

Chapter 4

Discussion

The present systematic review aimed to determine the imaging findings in auditory neuropathy spectrum disorder (ANSD). Three hundred seventy-nine research articles were initially selected for this systematic review to fulfill the aim. Based on the selection criteria, 19 studies were shortlisted. Several studies on the clinical characteristics and pathophysiology of ANSD have been published. However, not many focused on imaging findings in ANSD. This study focused on various imaging findings in the ANSD population across different age groups. Among the 19 shortlisted articles, 15 of the studies included the pediatric population as participants. One study solely described imaging characteristics of ANSD in adults, and the other three had children and adult participants. Furthermore, 14 studies included either bilateral ANSD or bilateral and unilateral ANSD conditions. Five studies focused only on unilateral ANSD characteristics.

4.1 Imaging abnormalities in the ANSD population

In the present systematic review, 18 studies showed an imaging abnormality in the ANSD population. However, one study showed that all the ANSD participants had no imaging abnormalities (Meethal et al., 2019). The most common imaging abnormality found in ANSD was cochlear nerve deficiency (CND), including cochlear nerve aplasia (CNA) and cochlear nerve hypoplasia (CNH), which was reported in more than half of the reviewed articles. Various imaging abnormalities reported in different studies are illustrated in Table 4.1

Table 4.1

Imaging abnormalities reported in ANSD across different studies

Imaging Findings	Studies
CND (CNA and CNH)	Laurent et al. (2022); Song et al. (2021); Lin et al. (2020) ; Rajput et al. (2019); Boudewyns et al. (2016); Mohammadi et al. (2015); Jeong & Kim (2013); Levi et al. (2013); Liu et al. (2012); Maris et al. (2011); Huang et al. (2010); Walton et al. (2008**);** Teagle et al. (2010); Buchman et al. (2006**)**
Vestibular-Labyrinthine abnormalities (cochlea, vestibule, SCCs or endolymphatic sac or duct)	Laurent et al. (2022); Lin et al. (2020); Rajput et al. (2019); Levi et al. (2013); Huang et al. (2010); Roche et al. (2010); Teagle et al. (2010); Walton et al. (2008**);** Buchman et al. (2006**).**
IAC Stenosis	Ai et al. (2016); Mohammadi et al. (2015); Levi et al. (2013); Huang et al. (2010); Roche et al. (2010); Walton et al. (2008); Buchman et al. (2006**).**
BCNC Abnormality	Jeong & Kim. (2013**);** Huang et al. (2010**);** Roche et al. (2010**).**
Intracranial abnormalities (forebrain, mid/hindbrain, CSF,WM)	Huang et al. (2010**);** Roche et al. (2010**);** Teagle et al. (2010).

CNS abnormalities	Lin et al. (2020); Rajput et al. (2019**)**
Smaller CN diameter and CSA	Peng et al. (2016**)**
Modiolar ossification (High modiolar attenuation)	Wang et al. (2017**)**

Note: CND-Cochlear nerve deficiency**,** CNA- Cochlear nerve aplasia**,** CNH-Cochlear nerve hypoplasia**,** IAC-Internal auditory canal, SCC-Semicircular canal, BCNC-Bony cochlear nerve canal, CNS-Central nervous system, CN-Cochlear nerve, CSA-Cross sectional area, CSF-Cerebrospinal fluid, WM-White matter

Various factors can contribute to the etiology of ANSD, and different sites will be involved in the pathological process. Abnormalities of the inner ear and brain are closely associated with CND due to the strong connection between the inner ear and the cochlear nerve (CN) development in fetal life and the brainstem influence in CN development. Also, the authors suggest that developmental insult to CN, inner ear, and rhombencephalon happen during earlier periods and lead to bilateral CND. In contrast, unilateral CND is associated with lesions within inner hair cells (IHC), spiral ganglion, or the CN, which occurs later in life (Huang et al., 2010). From Table 4.1, it can be noted that IAC stenosis and abnormal BCNC in association with CND are also common in ANSD. Glastonbury et al. (2002) report that IAC size may be related to the volume of vestibulocochlear nerve fibers. Also the BCNC size depends on how CN develops in utero. Human temporal bone studies explain CND in association with inner ear anomalies, narrow IAC, and very rarely concerning normal IAC (Felix & Hoffmann, 1985; Nadol & Xu, 1992; Nelson & Hinojosa, 2001; Spoendlin & Schrott, 1990; Ylikoski

& Savolainen, 1984). Lin et al. (2020) reported that inner ear abnormality found in their patients was related to prematurity (acquired ANSD), and CNS abnormalities were seen in acquired (Prematurity, Kernicterus & Perinatal hypoxia) and genetic-related ANSD.

Wang et al. (2017) report that the reason for modiolar ossification seen in ANSD is unclear; however, it can be due to neonatal insult, for example, hyperbilirubinemia which can cause changes in the otic capsule, including the modiolus, wherein the spiral ganglions are present. The mechanism responsible for CND is unclear; however, it can be due to congenital and acquired factors. The absence of neurotrophic factors can cause ganglion cell loss and CN agenesis (Bernd Paulette, 2008; Fritzsch et al., 2004). Some acquired insults to CN during the developmental period can also be suspected. Investigation of neurotrophic factors such as cytomegalovirus and other viruses and perinatal events is necessary. These reports highlight the need for detailed radiological evaluation in patients with ANSD characteristics to rule out coexisting pathology and to recommend correct management.

4.2. Different imaging protocols used for the etiology-based diagnosis of ANSD

Most studies in the present review employed Magnetic Resonance Imaging (MRI) as the primary imaging modality and/or a combination of Computerised Tomography (CT) and MRI to examine various abnormalities. None of the studies used CT alone. Details regarding the studies which employed MRI and a combination of CT and MRI are depicted in Table 4.2.

Table 4.2

Imaging modalities used in different studies

MRI	Combination of MRI and CT
Laurent et al. (2022)	Lin et al. (2020)
Song et al. (2021)	Wang et al. (2017)
Meethal et al. (2019)	Ai et al. (2016)
Rajput et al. (2019)	Mohammadi et al. (2015)
Boudewyns et al. (2016)	Jeong & Kim. (2013)
Peng et al. (2016)	Roche et al. (2010)
Levi et al. (2013)	Teagle et al. (2010)
Liu et al. (2012)	
Maris et al. (2011)	
Huang et al. (2010)	
Walton et al. (2008)	
Buchman et al. (2006)	

Liu et al. (2012) concluded that for the identification of CND, oblique sagittal MRI of IAC was most helpful in the precise diagnosis of the condition. Another study found that 3CNA, missed in CT, was confirmed through MRI (Mohammadi et al., 2015). Hence the authors suggest MRI as the first line of choice in the definitive diagnosis. A study on modiolar ossification in ANSD performed temporal bone CT and MRI utilizing mid-modiolar cut for the image analysis (Wang et al., 2017). Ai et al. (2016) used high-resolution CT (HRCT) temporal bone to identify IAC stenosis.

Peng et al. (2016) studied the short diameter (SD), long diameter (LD), and CSA of CN in adults with ANSD using 3.0 T MRI employing three-dimensional (3D) Fast Imaging Employing Steady-state Acquisition (FIESTA), and the images were reconstructed in the oblique sagittal plane. Few studies performed MRI using a dedicated VIII nerve protocol. Sagittal unenhanced T1-weighted images and axial fluid attenuation inversion recovery (FLAIR) and T2-weighted images through the brain, as well as high-resolution 3D constructive interference in the steady state (CISS) or fast recovery fast spin-echo (RESTORE) images through the temporal bones, was utilized (Roche et al., 2010; Huang et al., 2010). Roche et al. (2010) defined a small BCNC when the size is 1.3 mm or less in Temporal bone CT using contiguous direct sequential axial and coronal images. Buchman et al. (2006) reported that it is regarded as absent when the CN could not be seen on axial, coronal, or reconstructed coronal oblique IAC view.

Jeong and Kim (2013) classified ANSD as Type 1 and Type 2 based on the results obtained on CT. A normal BCNC on CT and CN on MRI were grouped into ANSD type 1, and patients with a narrow or obliterated BCNC on CT and a CND on MRI were regarded as ANSD type 2. It is unclear about the ideal imaging modality and criteria for labeling CND. Levi et al. (2013) report that the CT scan was superior for measuring IAC size and the BCNC, but MRI was superior for evaluating the nerve. Roche et al. (2010) recommend performing CT when a small IAC is evidenced. A normal IAC on CT does not always assure the presence of a CN (Walton et al., 2008). In light of this, it can be said that MRI is the preferred imaging technique for all children with ANSD. HRCT is used only when narrow IAC, pathology of the temporal bone, inner ear abnormalities, or

cochlear lumenal obstruction are found (Adunka et al., 2006, 2007; Buchman et al., 2006).

4.3 Cochlear nerve deficiency as a characteristic feature of unilateral ANSD

Studies on clinical characteristics, etiology and imaging findings in unilateral ANSD are limited (Laurent et al., 2022). Some studies solely report the clinical and imaging features of unilateral ANSD (Laurent et al., 2022; Song et al., 2021; Mohammadi et al., 2015; Liu et al., 2012; Maris et al., 2011), and few studies report CND as the predominant cause in unilateral ANSD (Mohammadi et al., 2015; Liu et al., 2012). Laurent et al. (2022) reported that 17 of their patients out of 18 with unilateral ANSD had CND (including CNA and CNH). Another study revealed that 59% of the participants with unilateral ANSD had evidenced CNA (Mohammadi et al., 2015). Also, Huang et al. (2010) reported that two-thirds of the unilateral ANSD participants in their study had CND. Liu et al. (2012) also suggest that CND may be an underlying mechanism for unilateral ANSD. Even though a few studies show an association between CND and unilateral ANSD, evidence in this area is lacking and unclear. Hence further investigations are necessary with more participants to better conclude the characteristic features and causes associated with unilateral ANSD. Also, these studies suggest the need for imaging rather than limiting audiological evaluation to understand better the pathology related to unilateral ANSD.

Chapter 5

Summary and Conclusions

The present study aimed to conduct a systematic review of imaging findings in ANSD. About 379 research articles were initially selected, and later 19 articles were finalized for the systematic review. Most studies used MRI as their imaging modality of choice to rule out various imaging abnormalities in ANSD. Most studies report cochlear nerve deficiency (CND) as a well-documented imaging abnormality associated with ANSD. Also, studies report the occurrence of CND in association with unilateral ANSD. However, the cause of unilateral ANSD is still unclear. Hence, more evidence in this area is necessary to conclude whether CND is a characteristic feature of unilateral ANSD. ANSD is a multifactorial condition encompassing heterogeneous etiologies. Therefore early imaging investigations add to explore the underlying mechanism in ANSD.

5.1 Implication of the Study

The topic of imaging findings in ANSD is both understudied and rarely investigated. This review identified some interesting findings regarding the imaging abnormalities evidenced in ANSD through CT and MRI. This review showed an association between CND and ANSD. Also, few unique studies explored on cochlear nerve diameter, cross sectional area and modiolar ossification in ANSD. Imaging investigation help to pinpoint the pathological site, and even the anatomic location of the site act as a variable CI outcome predictor. Thus, it can be implied from the present systematic review that integrating imaging studies into diagnostic protocol would help

understand the underlying pathology better and expedite decision-making and intervention.

5.2 Limitations of the Study

In this systematic review, only a few studies focused on unilateral ANSD. Also, most of the studies' sample size was small, especially those with unilateral ANSD. Many studies also had patients with comorbidities. Hence while extrapolating findings, it is crucial to remember that these results may not be generalizable to all individuals diagnosed with ANSD.

5.3 Future Direction

- More studies are required to draw firm conclusions regarding the association between CND and unilateral ANSD. .
- Interventional outcomes in CND can be a fruitful investigation.
- It is interesting to examine patients with CND with diffuse tensor imaging to determine whether these patients show significant changes in the fibers of the auditory tract.

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APPENDIX A

(NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the Study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. For exposures that can vary in amount or level, did the Study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			

APPENDIX B

(NIH) Quality Assessment Tool for Case-Control Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Did the authors include a sample size justification?			
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?			
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?			
6. Were the cases clearly defined and differentiated from controls?			
7. If less than 100 percent of eligible cases and/or controls were selected for the Study, were the cases and/or controls randomly selected from those eligible?			
8. Was there use of concurrent controls?			
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?			
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?			
11. Were the assessors of exposure/risk blinded to the case or control status of participants?			
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?			

APPENDIX C

(NIH) Quality Assessment Tool for Case Series Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?			
2. Was the study population clearly and fully described, including a case definition?			
3. Were the cases consecutive?			
4. Were the subjects comparable?			
5. Was the intervention clearly described?			
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?			
7. Was the length of follow-up adequate?			
8. Were the statistical methods well-described?			
9. Were the results well-described?			